DETAILED ACTION

Status of claims

The amendment filed on August 17, 2011 is acknowledged. Claims 1-8, 11, 20-22, 27, 34, and 36 are pending and under examination in this office action. It is noted that the status of claim 6 is incorrectly stated as "(withdrawn)". Since claim 6 was rejoined upon withdrawal of the requirement to elect a species of medical conditions in the last office action mailed on 3/17/2011, the status of claim 6 should not be indicated as "(withdrawn)".

Applicants' arguments, filed on August 17, 2011, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11, 20-22, 27, 34, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for delivering every and each immune response modifier (IRM) compound encompassed by claim 1 to various mucosal surfaces so as to achieve immunomodulation with reduced irritation of the mucosal surface from IRM compound by applying the IRM compound in repeated application to the mucosal surface and removing at least 50% of the IRM compound from the mucosal surfaces after each

application. In addition, claims 27, 34, and 36 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a specific condition associated with a mucosal surface such as cervical dysplasia with a IRM compound, does not reasonably provide enablement for the general treatment of conditions associated with any mucosal surface with interrupted delivery of the claimed IRM compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All factors have been considered together and specifically relevant factors are addressed below:

The instant claims are drawn to a method of delivering an immune response modifier (IRM) compound to a mucosal surface so as to achieve immunomodulation with reduced irritation of the mucosal surface from the IRM compound, comprising interrupted delivery of an IRM compound other than imiquimod by intermittently applying in repeated applications the IRM to the mucosal surface and, after each application, removing from the mucosal surface at least 50% by weight of the IRM that was originally applied in each application at a time before it would otherwise be naturally absorbed or eliminated. The claims are very broad since the claims

encompass delivering any IRM compounds, which have diverse chemical structures, and to any mucosal surfaces, which include any body surface with mucous membranes (mucosae) such as gastric mucosa, intestinal mucosa, bronchial mucosae, uterine mucosa, dendometrium, etc.

US 2002/0058674 (already made of record) teaches that some of the beneficial effects of IRMs are known, but the ability to provide therapeutic benefit via topical application of an IRM for treatment of a particular condition at a particular location may be hindered due to tissue irritation, formulation wash away, poor permeation or undesired systemic delivery of the topically applied compound ([0007]). US 2002/0058674 also teaches that topical application is often difficult or impossible due to the anatomical location of the tissue. In some cases, application of the agent to a general anatomical region that includes or surrounds the target tissue may be an alternative to direct topical application. But, if the agent has irritating properties, this alternative disadvantageously carries with it the possibility of irritating tissues surrounding the target tissue. In addition, even if the agent is non-irritating, regional application typically requires use of a greater volume or concentration of the agent to achieve a therapeutic result equivalent to that achieved by direct application to the target tissue ([0008]). In particular, the uterine cervix is one example of a target tissue to which it is difficult to apply a topical agent. Relative to a standing position, the cervix is typically located at the uppermost portion of the vaginal cavity. However, while the cervix is located at the uppermost portion of the vaginal cavity, age, the stage of the estrous cycle, pregnancy, and other factors cause variability of the location of the cervix between different women and in the same woman at different stages of life ([0009]). In addition, with the exception of certain body orientations, gravity tends to drain agents away from the cervix. Normal discharge and flow of fluids, both menstrual and non-

menstrual, also drain away from the cervix ([0011]). Theses teachings demonstrate the difficulty of delivering an appropriate amount of IRM compounds to various mucosal surfaces for optimal treatment with reduced irritation and predicting how much amount of a given IRM compound is naturally absorbed or eliminated from a target mucosal surface after each application.

The absorption or elimination of a given IRM compound applied to mucosal surface can vary depending on various factors: types of IRM compounds, formulation types, types of mucosal surfaces, the size or location of application area, individual patient's condition or body metabolism rate (e.g. some people have faster elimination capacity of drugs), even whether the patient is upright or not as stated above. Thus, such variety of factors would reasonably affect the amount of IRM compounds that would be either absorbed or eliminated naturally at each delivery episode. This multitude of factors indicate that prediction of timing of removing the IRM as claimed would be so complex as to support undue experimentation for practicing the instant invention in order to satisfy the percentage removal limitation in the claims as well as what time would be predictable. In addition, none of the examples in the specification as filed support a practice that meets the instant claim limitation. The specification only discloses removing the IRM compounds 2, 4, and 6 hours after application (p20-29), however there is no information or measurement as to how much amount of the IRM compound is removed at those times. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose specific details as to how to perform the claimed removing step and the timing of removing a given IRM compound to satisfy the percentage removal limitation in the claims for various IRM compounds with diverse chemical structures and different mucosal surfaces which would affect

the amount of IRM compounds either absorbed or eliminated at each delivery episode while achieving the desired therapeutic effects as claimed. Neither the teachings in the art nor the specification provide any direction or guidance so that a person of ordinary skill in the art would be able to practice the claimed complex delivery method without undue experimentation.

In addition, the instant claims 27, 34, and 36 are drawn to the treatment of any conditions associated with any mucosal surfaces, i.e. any types of conditions or disorders occurring in mucosal surface, which may have different etiologies and pathophysiologies including those not associated with immune response such as genetic mucosal disorders (e.g. multiple cutaneous and mucosal venous malformations). IRM compounds act through basic immune system mechanisms known as toll-like receptors to induce selected cytokine biosynthesis. For example, imiquimod, which is a well-known IRM compound, is being used for treating actinic keratoses, superficial basal cell carcinoma, and external genital warts. However, there is no prior art teaching that IRM compounds are generally useful for all the mucosal conditions including such genetic mucosal disorders. Although the specification discloses the effect of IRM compounds on the production of certain cytokines such as TNF and MCP-1, it does not provide any working examples for the treatment of any mucosal conditions. There is no demonstrated correlation that the tests and results disclosed in the specification apply to all types of mucosal conditions or disorders embraced by the instant claims. Furthermore, it is not reasonable to any agent to be able to treat any mucosal conditions or disorders generally regardless of etiologies.

Generally, the relative skill of those in the art of pharmaceuticals and pharmacology is high. However, Applicant has not provided any competent evidence or disclosed tests that are highly predictive for practicing the claimed method for accomplishing the desired result of the

claimed invention without undue experimentation. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970).

Due to the large quantity of experimentation necessary to determine how to practice the claimed method, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, and the breadth of the claims, undue experimentation would be required of the skilled artisan to practice the claimed invention in its full scope, with no assurance of success..

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

Response to Applicants' argument:

Applicants argued that claims, particularly as amended, are fully enabled and that it would not require undue experimentation for one skilled in the art to practice the claimed invention. Applicants further stated that the claimed compounds are small molecules that work through a common mechanism of action in the immune system (activating through TLRs 6, 7, and/or 8). Also, Applicants argued that there is no reason one skilled in the art would doubt that general usefulness and applicability of IRM compounds for treating diseases generally on mucosal surfaces and nor would one skilled in the art doubt the benefits of being able to proactively remove the IRM from contact with a mucosal surface to reduce side effects or that

this discovery would be generally applicable and useful. In addition, Applicants argued that with knowledge of the present application in mind, it would not require any undue experimentation to practice the claimed invention.

Applicants' arguments were fully considered but are not found to be persuasive.

First, Applicants did not address the lack of sufficient enabling disclosure for applying every and each immune response modifier (IRM) compound encompassed by claim 1 in repeated application to various mucosal surfaces and removing at least 50% of the IRM compound from the mucosal surfaces after each application while achieving immunomodulation with reduced irritation of the mucosal surface from IRM compound. As stated in the last office action mailed on 3/17/2011, the absorption or elimination of a given IRM compound applied to mucosal surface can vary depending on various factors: types of IRM compounds, formulation types, types of mucosal surfaces, the size or location of application area, individual patient's condition or body metabolism rate (e.g. some people have faster elimination capacity of drugs), even whether the patient is upright or not as evidenced by US 2002/0058674. Thus, such variety of factors would reasonably affect the amount of IRM compounds that would be either absorbed or eliminated naturally at each delivery episode. This multitude of factors indicate that predicting the timing of removing each and every IRM compound for meeting the percentage removal limitation (at least 50%) after each application while achieving immunomodulation with reduced irritation of the mucosal surface as claimed would be so complex and unpredictable as to support undue experimentation for practicing the claimed method. In addition, none of the examples in the specification as filed support a practice that meets the instant claim limitation. The specification only discloses removing the IRM compounds 2, 4, and 6 hours after application

(p20-29), however there is no information or measurement as to how much amount of the IRM compound is removed at those times. Furthermore, there is no guidance or information how to estimate or predict the timing of removing a given IRM compound to ensure that at least 50% of the IRM compound can be repeatedly removed after each application while achieving immunomodulation with reduced irritation of the mucosal surface as claimed. For the purpose of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose specific details as to how to perform the claimed removing step and the timing of removing a given IRM compound to satisfy the percentage removal limitation in the claims for various IRM compounds with diverse chemical structures and different mucosal surfaces which would affect the amount of IRM compounds either absorbed or eliminated at each delivery episode while achieving the desired therapeutic effects as claimed. Neither the teachings in the art nor the specification provide any direction or guidance so that a person of ordinary skill in the art would be able to practice the claimed complex delivery method without undue experimentation.

In addition, there is no prior art teaching that IRM compounds are generally useful for all the mucosal conditions including genetic mucosal disorders (e.g. multiple cutaneous and mucosal venous malformations), which are not caused by abnormality in immune response as stated in the last office action mailed on 3/17/2011. The fact that even a well-known IRM compound such as imiquimod, which activates toll-like receptors as claimed, does not prove to be effective for all the mucosal conditions including such genetic mucosal disorders supports that it is not reasonable for any IRM compound to be able to treat all mucosal conditions or disorders generally regardless of etiologies. Furthermore, while the specification discloses the effect of

IRM compounds on the production of certain cytokines such as TNF and MCP-1, it does not provide any working examples for the treatment of any mucosal conditions with the claimed interrupted delivery method. There is no demonstrated correlation that the tests and results disclosed in the specification apply to all types of mucosal conditions or disorders embraced by the instant claims.

Furthermore, Applicant did not provide any evidence to support Applicants' assertion that claims as amended would not require undue experimentation for one skilled in the art to practice the claimed method. It should be noted that arguments of counsel cannot take the place of factually supported evidence. See MPEP 2145.

The following rejection is necessitated by the amendment to claims (i.e., cancelation of claim 17)

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is improperly dependent from canceled claim 17, thus rendering the claims indefinite. For the compact prosecution, claim 20 is treated to be dependent from claim 1 for the compact prosecution.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00 am-6:00 pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BONG-SOOK BAEK
Examiner, Art Unit 1629

/Bbs/

/James D Anderson/
Primary Examiner, Art Unit 1629